REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. EXAMINER INTERVIEW

Applicants are grateful for the personal interview held November 9, 2004 between Applicants' representative, Jay Williams, and Examiner Mitra and Supervisory Patent Examiner Webber.

During the interview, it was indicated that the specification enables claims to a fusion of a binding protein and the reporter proteins exemplified in the specification, such as Green Fluorescent Protein (GFP) and alkaline phosphatase, or any others demonstrated in the specification or the state of the art. The Examiners suggested amending the claims to a fusion of a binding protein and the reporter proteins exemplified in the specification, such as Green Fluorescent Protein (GFP) and alkaline phosphatase, or any others demonstrated in the specification of the state of the art. The claims have been amended in accordance with the Examiner's suggestion.

The Examiners also clarified that claims 27 and 28 are allowed.

II. CLAIM STATUS & AMENDMENTS

Claims 1 and 3-28 were pending in this application when last examined.

Claims 10-13 and 15-26 were withdrawn as non-elected subject matter.

In item 6 on page 1 of the Office Action, it is indicated that claims 1, 3, 4, 6, 7 and 14 were rejected. However, kindly clarify the status of claim 14, because this claim was not included in a rejection. Instead, it was objected to.

Claims 3-5, 8, and 14 were objected to.

In item 5 on page 1 of the Office Action, claims 27 and 28 were indicated as allowed with thanks.

Claims 1, 6, 7, 11, 12 and 27 have been amended.

Support for the Fluorescent protein added to claims 1, 7, 11 and 12 can be found in original claims 4 and 6 and in the specification, for example, at page 7, lines 2-12, page 8, lines 3-9, page 25, line 2 to page 31, line 11 (Examples 1 and 2) and Figs. 2, 3 & 7. Furthermore, the use of flourescent proteins is further supported by the state of the art as evidenced by U.S. Patent No. 6,469,154 as will be discussed below.

Support for the kanamycin nucleotidyltransferase added to claims 1, 11 and 12 can be found in the specification, for example, at page 23, line 9 to page 25, line 1.

Support for the alkaline phosphatase added to claims 1, 11 and 12 can be found in original claim 5 and in the specification, for example, at page 31, line 17 to page 33, line 9 (Example 3).

Support for the minor editorial changes in claims 6, 7 and claim 27 can be found in the claims as originally filed.

Therefore, no prohibited new matter has been added by this amendment.

Claims 4-5 and 8 have been canceled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional application on any canceled subject matter.

Thus, upon entry of this amendment, claims 1, 3, 6, 7 and 9-28 will be pending.

It is respectfully submitted that the foregoing amendments and the following arguments are deemed to overcome the outstanding rejections. Thus, Applicants respectfully request that withdrawn method claims 11, 12 and 14 be rejoined with the elected product claims. In this regard, kindly note that claims 11 and 12 were amended to conform with the language of amended claim 1.

III. OBJECTION TO THE CLAIMS

Claims 3-5, 8, and 14 were objected to as including non-elected species and being dependent on non-elected claims. See Office Action, page 2, 2nd paragraph.

It is respectfully submitted that the present amendment overcomes this objection. Again, Applicants respectfully request that withdrawn method claims 11, 12 and 14 be rejoined with the elected product claims.

IV. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1, 3, 4, 6 and 7 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification is enabling for specific fusion proteins only, and not a fusion of any binding protein and any reporter protein. See Office Action, pages 4-6. It is noted that claim 14 was not included in this rejection.

It is respectfully submitted that the present amendment overcomes this rejection for the following reasons.

During the interview, it was indicated that the specification enables claims to a fusion of any binding protein and the reporter proteins exemplified in the specification, such as Green Fluorescent Protein (GFP) and alkaline phosphatase, or any others demonstrated in the state of the art. The claims have been amended in accordance with this suggestion.

Also, during the interview, it was indicated that the "mutant" and "fragment" language is permitted in view of the additional functional limitations in the claims.

With regard to the reporter protein, the claims have been amended to "flourescent protein" which is exemplified in the specification and demonstrated in the art. It is respectfully submitted that the specification enables the full scope of "fluorescent proteins" as the reporter protein added to amended claims 1, 7, 11 and 12.

It is noted that the test of enablement is whether one reasonably skilled in the art could make or use the invention based on the disclosure in the specification coupled with the knowledge in the art without undue experimentation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See M.P.E.P. § 2164.01.

In the instant case, the teachings of the specification coupled with the knowledge in the art regarding fluorescent proteins, fully enables the use of fluorescent proteins in the claimed invention as reporter proteins.

In this regard, the specification exemplifies the use of a fluorescent protein (i.e., the Green Fluorescent Protein (GFP)) at page 7, lines 2-12, page 8, lines 3-9, page 25, line 2 to page 31, line 11 (Examples 1 and 2) and Figs. 2, 3 & 7.

Furthermore, the use of fluorescent proteins as reporter proteins is supported by the knowledge in the art as evidenced by U.S. Patent No. 6,469,154, a copy of which is enclosed. In this regard, US '154 discloses a sensor protein comprising a reporter protein and a binding protein wherein the reporter protein is Fluorescent Protein. For instance, at column 10, lines 16-32 of US '154, a wide variety of common fluorescent proteins are disclosed, including the Green Fluorescent Protein (GFP), the Blue Fluorescent Protein (BCP), the Yellow Fluorescent Protein (YFP), and the Cyan Fluorescent Protein (CFP).

Similarly, at column 39, lines 2-21, in a section concerning the "Cloning and Gene Construction" in the Example of US '154, the construction of a YFP is described as follows:

> Yellow GFP mutants (YFPs) with peptide insertions replacing Y145 were made by performing two separate polymerase chain reactions (PCRs). The first PCR amplified the N terminal piece of YFP to include a 5' BamH1 site and 3' replacement of Y145 with the hexapeptide linker GGTGEL (coded for by DNA containing Kpnl and Sacl restriction sites for subsequent cloning). The second PCR amplified the C terminal piece of YFP to include the 5' linker (GGTGEL) replacing Y145 and a 3' EcoRl site. These two PCR products were combined and amplified with N and C terminal YFP primers to yield a full length cDNA containing the insertion. The full length cDNA was restricted with BamH1 and EcoRl, ligated and cloned into the BamH1 and EcoRl sites of pRSET B (Invitrogen) to yield the plasmid pYFPins. Next, the cDNAs for Xenopus Calmodulin and the first zinc-finger motif from zif268 were amplified with PCR using primers containing 5' Kpn1 sites and 3' Sacl sites and digested with Kpn1 and Sacl. Finally, insertions into YFPs were made by cloning cDNAs of inserted proteins in between the Kpn1 and Sacl sites of pYFPins. (FIG. 1).

Further, at column 39, lines 34-45 in the section concerning the "Protein Titrations" in the Example of US '154, it is described that:

> Calcium titrations of YFP-Calmodulin insertion proteins were done in a cuvette in a fluorescence spectrometer in 100 mM KCl, 10 mM MOPS at pH 7.5 (buffer was run through a Chelex column to remove traces of calcium). Small aliquots of $CaCl_2$ were added to this cuvette and a full fluorescence emission spectrum was taken after each addition. (FIG. 2b, FIG. 3).
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> Zinc titrations of YFP-zinc finger insertions were done in 50 mM MOPS, pH 7.0. A fluorescence emission spectrum was taken of the protein in buffer containing 50 uM EDTA, and then small aliquots of $ZnCl_2$ were added, and subsequent spectra were recorded. (FIG. 4).

Accordingly, US '154 discloses a sensor protein where a Xenopus Calmodulin or a zinc-finger motif is inserted into YFP which is a mutant of GFP. The enablement of such a construct is confirmed by the Examples of US '154. Thus, it is clear that such a construct utilizing the broad fluorescent proteins has already been deemed to be enabled by the PTO. See, for instance, claim 1 of US '154.

Based on such knowledge in the art and the disclosure of the instant application, it is clear that the broader Fluorescent Protein is fully enabled. In this regard, given the teachings and examples in the specification coupled with the knowledge in the art, one of skill in the art could make and use the full scope of type of fluorescent proteins, such as GFP or YFP, without undue experimentation.

In view of the above, the rejection of claims 3, 4, 6, and 7 under 35 U.S.C. § 112, first paragraph, is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is in condition for allowance and early notice to that effect is hereby requested.

If it is determined that the application is not in condition for allowance and the Examiner has proposals for expediting allowance, the Examiner is invited to telephone the undersigned attorney at the number below.

Respectfully submitted,

Hiroshi YANAGAWA et al.

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/JFW/ksh
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
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